REMARKS

The Office Action and the cited and applied references have been carefully reviewed. No claim is allowed. Claims 1-3 and 6-32 presently appear in this application and define patentable subject matter warranting their allowance. Reconsideration and allowance are hereby respectfully solicited.

Claims 1-7, 10, 12 and 13 have been rejected under 35 U.S.C. §102(b) as being anticipated by Diamond et al., *Hippocampus*, 9:542-552 (1999). The examiner states that "Diamond teaches rats conditioned to exhibit recurrence of trauma upon repeated exposures to a cat… As there are no structural differences between the animals claimed and those of Diamond, the particular phenotypes claimed, Wolframin and Sigma 1 receptor levels or having 2 or 3 [Post-traumatic stress disorder (PTSD)] PTSD behaviors would be inherent to the rat of Diamond." The examiner further reiterates the protocol used by Diamond: a baseline level was established for 12 rats prior to exposure to a cat; after the baseline was established, the rats were retested in the six-arm maze every day for 6 six days after exposure to the cat; error rates were measured as the mean average of the group of rats tested and the determinations were made by comparing the rats together. The examiner takes the position

that Diamond anticipates the claimed invention. This rejection is respectfully traversed.

Applicants wish to emphasize that the animal model for PTSD disclosed in the present application was, at the time the invention was made, the only such model that closely resemble PTSD in humans. A human having experienced a traumatic event may, or may not, develop PTSD following a similar experience which can occur many years after the initial trauma. For example, a soldier having experienced shelling in battle, may develop PTSD just by being exposed to a similar noise years after the battle. This is referred to as memorizing. On average, about 20% of the individuals exposed to a traumatic event, will develop PTSD following a re-exposure to a traumatic-like event.

According to the model of the present invention, the animals are exposed to a trauma event in the form of litter with a cat scent. At least one week later, the animals were re-exposed to cat litter, but this time without cat scent. Therefore, this is a trauma-like event. The animals were then re-re-exposed to the trauma-like event four weeks after the initial trauma event, and only then were the animals examined for PTSD. These animals are considered to suffer from chronic trauma.

By contrast, in Diamond, the rats were exposed to a cat on the first day and also on each of the following 5 days of the

experiment, i.e., the re-exposure was to the same trauma and not to a trauma-like event (page 545, first column, 3rd paragraph). Furthermore, each re-exposure occurred a short time after the previous exposure to the trauma and therefore no memorizing is involved. Diamond's animals suffer from acute trauma, which is a completely different physiological state than chronic trauma. The inventor has data showing that the levels of the steroid Dehydroepiandrosterone (DHEA) are differentially regulated in the brains of animals with chronic and acute trauma. This data can be provided in a declaration if the examiner deems it necessary.

It is important to note that only about 20% of the animals treated according to the method of the present invention develop PTSD (see Table 4), which is also the case for humans exposed to a trauma event and then re-exposed to a trauma-like event. The model of the present invention therefore reflects the situation in human PTSD very well. In models creating acute trauma in animals, such as in Diamond, 50-70% of the animals exposed to a traumatic event develop anxiety with PTSD-like symptoms and therefore these models do not reflect the situation in human PTSD.

Claim 1 is amended to better define the present invention. The animals are now characterized by all three PTSD-like behaviors, and not just by at least one of them, since this

is an absolute requirement of the model. New claims 28-30 are added that better define and further distinguish the animals of the present invention from those of the cited prior art by defining the parameter used to measure the behaviors (freezing in claim 28) and the temporal aspects of the model (claims 29 and 30).

For the reasons discussed above, the particular phenotypes claimed, Wolframin and Sigma 1 receptor levels or having 2 or 3 PTSD behaviors would not be inherent to the rat of Diamond and therefore the presently claimed invention is not anticipated by Diamond.

Reconsideration and withdrawal of the rejection are therefore respectfully requested.

Claim 15 has been rejected under 35 USC 102(b) as being anticipated by or, in the alternative, under 35 U.S.C. §103(a) as being as obvious over Diamond et al.

As stated above, claim 15 is dependent on claim 6 drawn to a method for producing the maladapted animals of the invention. The examiner is of the opinion that since the animals of the invention are anticipated by Diamond, the animal claimed is seen as the rat of Diamond produced by a different method. The examiner asserts that if the product in the product-by-process claim is the same as or obvious from a product of the

prior art, the claim is unpatentable even through the prior product was made by a different process. This rejection is respectfully traversed.

For the same reasons as discussed above with regard to the presently claimed non-human animal model as the product, the presently claimed product-by-process is also not anticipated or made obvious by Diamond.

Reconsideration and withdrawal of the rejections are therefore respectfully requested.

Claims 6 and 8 have been rejected under 35 U.S.C. §103(a) as being unpatentable over Diamond in view of Cohen et al., *Eur. Neuro. Psychopharmacology*, 10:429-435 (2000). The examiner states that "Cohen teaches stress hormones, such ATCH and corticosterone, alter after experiencing chronic stress…Cohen also teaches in PTSD patients the conventional thought is cortisol is reduced …[and that] rats exposed to cat scent once, produced the generalized anxiety seen in PTSD patients." The examiner is thus of the opinion that Cohen offers teachings, suggestions and motivation to determine plasma levels of ATCH, corticosterone and cortisol in rats exhibiting PTSD behavior. The examiner holds that it would have been obvious to the ordinary artisan to produce rats exhibiting a PTSD behavior as taught by Diamond and further determining the effect of traumatic

stress on plasma levels of ATCH, corticosterone and cortisol. This rejection is respectfully traversed.

Cohen exposes the rats once to cat smell (page 430, second column, 5th paragraph). These animals have therefore not yet developed PTSD. Since, as argued above, Diamond does not teach the production of rats exhibiting PTSD behavior, and Cohen measures plasma levels of ATCH, corticosterone and cortisol in animals that have not yet developed PTSD, this rejection is irrelevant and the combination of applied references cannot lead one of ordinary skill in the art to the presently claimed invention.

Reconsideration and withdrawal of the rejection are therefore respectfully requested.

Claims 6, 10 and 11 have been rejected under 35 U.S.C. §103(a) as being over Diamond in view of Adamec et al. *Physiology and Behavior*, 65:723-737 (1999). The examiner states that "Adamec teaches determining passive behavior in cat-exposed rats by analyzing videotapes of rat-cat interactions for freezing…" The examiner takes the position that it would have been obvious to one of ordinary skill in the art at the time of the instant invention to produce rats as taught by Diamond and analyze them for freezing as taught by Adamec. This rejection is respectfully traversed.

The fact that freezing may be used to measure all three behaviors required to define an animal as mal-adapted is a finding of the present invention. Adamec measured freezing during a single exposure to a cat (page 725, first column, 2nd paragraph) and not after many weeks as in the present invention. No re-exposure was performed. Therefore, the rats of Adamec were under acute trauma. Also, as noted by the examiner, freezing was measured as a measure for passive defense (page 725, first column, paragraphs 5 and 6). The examiner however fails to take note of the fact that freezing was found not to be affected by anxiolytic drugs (page 734, first column, paragraph 5), and therefore one of ordinary skill in the art would not use freezing as taught by Adamec as a measure for anxiety, and even less so, for PTSD. Since Diamond does not teach the production of rats exhibiting PTSD behavior and Adamec does not teach how to measure PTSD behavior, the combination of Diamond and Adamec cannot lead one of ordinary skill in the art to the present invention.

Reconsideration and withdrawal of the rejection are therefore respectfully requested.

It is noted that although all claims were indicated as rejected on the Office Action Summary page, no specific comments were made by the Examiner regarding claims 9, 14 and 16-27.

In view of the above, the claims comply with 35 U.S.C. §112 and define patentable subject matter warranting their allowance. Favorable consideration and early allowance are earnestly urged.

Respectfully submitted,

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